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Clinical aspects of allergic disease

Cetirizine in patients with seasonal rhinitis and concomitant asthma: prospective, randomized, placebo-controlled trial

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Objective: This study explored the safety and efficacy of cetirizine for treatment of allergic rhinitis and asthma.

Methods: Daily treatment for 6 weeks with cetirizine 10 mg (93 patients) was compared with placebo treatment (93 patients) in a randomized, double-blind parallel study of patients with allergic rhinitis and asthma. This multicenter study was started just before onset of the fall pollen season. Rhinitis and asthma symptoms were assessed twice daily; spirometry was performed weekly.

Results: Placebo-treated patients experienced a worsening of rhinitis symptoms from baseline throughout the study, whereas cetirizine-treated patients had a significant improvement in rhinitis symptoms at week 1, which was maintained after onset of the pollen season. Asthma symptoms in the cetirizine group improved from baseline at week 1; symptoms were significantly better than in the placebo group for 5 of 6 weeks of the study. Pulmonary function did not worsen in patients taking cetirizine or placebo; there were no differences between treatments as determined by spirometry. Albuterol use was less frequent in the cetirizine-treated patients for every week of the study, but differences did not reach significance. Pseudoephedrine use was similar in both groups. More cetirizine-treated patients (90%) completed the trial than did placebo-treated patients (74%). Both treatments were well tolerated.

Conclusion: Cetirizine 10 mg daily is safe and effective in relieving both upper and lower respiratory tract symptoms in patients with seasonal allergic rhinitis and concomitant asthma. (J ALLERGY CLIN IMMUNOL 1995;95:923-32.)

Key words: Allergic rhinitis, asthma, antihistamines, cetirizine, histamine₁-receptor antagonists, histamine, placebo, prophylaxis

Abbreviation used
bid.: Twice daily

Allergic rhinitis is a relatively common disorder in the general population, as is asthma: these disorders affect approximately 20 and 10 million Americans, respectively.¹ Various epidemiologic surveys have demonstrated that allergic rhinitis and asthma frequently coexist,¹⁻⁴ that these disorders are on the rise despite effective treatment and known preventive methods,^{1,2} and that familial and environmental influences may be involved.^{1,5} In fact, allergic rhinitis may be a risk factor for asthma.⁴ Outcome data in patients with allergic rhinitis and asthma have not been encouraging: only 10% of patients are cured; symptoms are ameliorated in 50%; and 40% of patients have either no improvement or worsening of their conditions.²

Histamine, an important mediator in both allergic rhinitis and asthma, causes smooth muscle contraction, increased secretion of mucus, increased vascular permeability leading to mucosal edema, and parasympathetic nerve stimulation.⁶⁻¹³ Released by a number of stimuli, histamine levels are elevated in the peripheral circulation and lungs of patients with asthma because of increased peripheral basophil and mast cell degranulation. Inhalation of histamine can cause bronchospasm in most individuals, but the response of patients with asthma is increased and correlates with hyperreactivity.¹⁰⁻¹¹ Elevated plasma histamine levels occur with both the early and late asthmatic responses to antigen challenge and in patients with spontaneously occurring asthma.^{6,7}

The early- and late-phase reactions to antigen bronchial challenge, which are produced by different mechanisms, mimic the phases of asthma. The immediate reaction is primarily due to a bronchospastic component, whereas the late-phase reaction is principally an inflammatory reaction that develops over time. Increased histamine levels may contribute to airway hyperreactivity and chronic asthma. Through the action of infiltrating eosinophils and other cells, the late-phase inflammatory reaction may contribute to chronic symptoms in severe asthma (e.g., nonspecific bronchial hyperreactivity, submucosal edema) after repeated exposure to an allergen.⁷

In 1949 Herxheimer¹⁴ showed that antihistamines had some utility in the management of

asthma. Despite the importance of histamine in the pathophysiology of asthma, the early antihistamines were not considered of value in its treatment because they were not effective in doses recommended for allergic rhinitis, because higher doses resulted in intolerable side effects, and because side effects limited their use intravenously or via aerosol.⁶⁻⁹ This could be attributed to the low potency of drugs and their ability to react with many different receptors. There are few reports of bronchoconstriction caused by antihistamines.^{15, 16} The approved labeling for many antihistamines included a warning that they not be used in patients with asthma because of concern that they may cause thickening of mucus and bronchoconstriction of airways. However, the American Academy of Allergy and Immunology has recommended that the warning be deleted from antihistamine labeling and that these drugs be prescribed to asthmatic patients when otherwise indicated, unless a patient has previously had an adverse reaction.¹⁷ One of the newer agents, cetirizine, is more selective and is effective over a wide range of dosages. Some evidence suggests that several of the newer agents may be useful in treating asthma.^{6-8, 18-29} It is now established that the H₁-specific antihistamines can be used safely in most patients with asthma.

Cetirizine is among the newer H₁-specific receptor antagonists. It is a potent antihistamine,²⁹⁻³³ and it inhibits allergen-induced eosinophil chemotaxis.³⁴⁻³⁶ It does not have effects on calcium channels, or serotonin, dopamine, α_1 , and muscarinic receptors,³⁷ and, in isolated human bronchi, it has been shown to potentiate the bronchodilator effect of albuterol.³⁸ These effects suggest that cetirizine is potentially well suited for the treatment of asthma, and a beneficial effect has been shown or suggested in several studies.^{6, 24-31, 39-44} In addition, cetirizine is well tolerated, minimally crosses the blood-brain barrier,^{29, 37} and as a metabolite of hydroxyzine, is not further metabolized extensively. Cetirizine was found to have no electrocardiographic effects.⁴⁵

This study was conducted to determine the safety and efficacy of cetirizine compared with placebo when administered to patients with a history of allergic rhinitis and mild to moderate bronchial asthma. In this study cetirizine was administered at a dose of 10 mg daily, the most frequently used dose for the treatment of allergic rhinitis.

METHODS

This 6-week multicenter, randomized, double-blind, placebo-controlled parallel study was conducted shortly

before (in most cases 1 to 2 weeks) and during a well-defined regional fall pollen season for each center in 1991. Male or female subjects (postmenopausal or nonpregnant, nonlactating, practicing an effective method of birth control), aged 12 to 70 years, with a history of seasonal allergic rhinitis that became symptomatic during the same annual pollen season and mild to moderate bronchial asthma were eligible for enrollment. At study entry, patients had to have documented hypersensitivity to a local seasonal allergen, as determined by skin test or RAST within 2 years, and at least 3 of the following signs or symptoms of rhinitis: sneezing, nasal congestion, itchy eyes or nasal mucosa, postnasal discharge, watery nasal discharge, or watery eyes. In addition, within 3 years of study entry, patients had to have a documented forced expiratory volume in 1 second between 50% and 80% of their predicted value and at least a 15% improvement from baseline after administration of a bronchodilator.

Patients were excluded from the study if they had symptoms of moderate to severe rhinitis or asthma, another concomitant illness that might interfere with the evaluation of clinical response, history of intolerance to antihistamines or bronchodilators, history of a neuropsychiatric disorder requiring therapy, history of alcohol or drug abuse, previous participation in a cetirizine clinical trial, or receipt of an investigational drug within the previous month. Patients were required to withhold drugs that might interfere with the study such as systemic or topical corticosteroids and cromolyn sodium for a week, antihistamines for 3 days, and astemizole for 6 weeks.

The study protocol was approved by an institutional review board at each site, and written informed consent was obtained from all patients or from the parent or legal guardian if the patient was a minor.

Treatment protocol

Patients were randomized to treatment with cetirizine 10 mg or matching placebo once daily in the morning. After the first daily peak flow measurement had been taken, treatment was initiated and continued for 6 weeks. Pseudoephedrine 30 mg every 6 hours was allowed as rescue medication for control of nasal congestion. Asthma was controlled with albuterol administered on an as-needed basis by metered-dose inhaler; oral theophylline was allowed if patients were receiving a stable dose before the study. No other asthma medications were allowed.

All patients underwent prestudy screening that included RAST or skin testing to confirm hypersensitivity to seasonal allergen pollen, if not documented within 2 years of study entry; chest x-ray studies, if none were performed in the year preceding study entry; laboratory tests, including complete blood count with differential, liver and kidney function tests, and urinalysis; pregnancy test in women of child-bearing potential; and serum theophylline level in patients receiving theophylline.

At baseline (2 weeks before anticipated local allergen pollination), a complete medical history including allergic history, limited physical examination, pulmonary function testing before and 15 minutes after 2 inhalations of albuterol from a metered-dose inhaler, and an assessment of signs and symptoms were done. If patients were receiving medications prohibited by the protocol such as topical or systemic corticosteroids, cromolyn, or other antihistamines, they completed an adequate wash-out period. Patients who met all eligibility requirements at the baseline visit were dispensed medication and a diary in which dosing and daily overall symptoms were to be recorded.

During the study treatment period, patients returned weekly at the same time of day for evaluation of symptoms and adverse events, review of diaries, pulmonary function testing before and after albuterol administration, evaluation of compliance, and dispensing of new diary and medication supply. At the end of week 6, baseline parameters were repeated along with global evaluations by patient and investigator.

Pollen counts were performed at each site, and the day of onset of the local pollen season was documented by each site.

Efficacy measures

Using a MiniWright meter (MiniWright, Columbus, Ohio), patients measured their peak flow in the morning and evening (before and 15 minutes after bronchodilator inhalation). After each measurement, patients rated on a 10-point scale (0 = no symptoms to 9 = unbearable symptoms) selected symptoms of both rhinitis and asthma that had been experienced in the previous 12 hours. Symptoms and signs of rhinitis included sneezing, nasal congestion, itching of nose and eyes, postnasal drip, runny nose, and watery eyes; symptoms of asthma included chest tightness, wheezing, shortness of breath, cough, sputum production, and nocturnal asthma. Patients recorded their ratings and the number of inhalations of bronchodilator, the number of pseudoephedrine tablets, and any other medications consumed in the previous 12-hour period in their diaries.

At the end of the study, patients and investigators completed global evaluations of the efficacy of treatment with respect to rhinitis and asthma on a 5-point scale (1 = excellent control of symptoms to 5 = poor control of symptoms). Patients also rated personal satisfaction with treatment on a 5-point scale (1 = exceptionally well satisfied to 5 = unsatisfied).

Statistical methods

The mean symptom scores, peak flow measurements, and drug usage were determined weekly. The key efficacy parameters of asthma and rhinitis symptoms, albuterol and pseudoephedrine use, and pulmonary function variables were compared with standard analysis of variance procedures to determine the

TABLE I. Baseline demographics and disease characteristics

Characteristic	Cetirizine (n = 93)	Placebo (n = 93)
Sex		
Male	41	41
Female	52	52
Race		
White	76	81
Other	17	12
Age (yr)	27.7 ± 11.3	29.0 ± 11.9
Duration of illness (yr)	18.1 ± 9.6	18.0 ± 10.8
Total rhinitis symptom score	5.8 ± 3.3	6.6 ± 3.3
Total asthma symptom score	5.2 ± 5.1	5.9 ± 6.0
Percent predicted FEV ₁		
50 to 64	2 (2)*	2 (2)
65 to 84	59 (63)	51 (55)
85 to 99	25 (27)	34 (37)
100 to 119	5 (5)	6 (6)
≥120	2 (2)	0 (0)
Percent change FEV ₁ after/before albuterol		
≤ -5	1 (1)	3 (3)
-4 to +4	26 (28)	16 (17)
+5 to +14	36 (39)	46 (50)
≥ +15	30 (32)	28 (30)
Prior theophylline use	21 (23)	27 (30)

FEV₁, Forced expiratory volume in 1 second.

*Number in parentheses = percent of patients.

relative efficacy of cetirizine. Statistical significance was declared at a *p* value of less than 0.05 as determined by a two-tailed *t* test.

RESULTS

Of the 186 patients who participated in the study, 93 were randomized to cetirizine treatment and 93 to placebo treatment. With respect to demographic and disease characteristics, including rhinitis and asthma symptom scores, pulmonary function, and theophylline use, there were no statistically significant differences between groups at baseline (Table I).² The number of patients completing the study was significantly (*p* = 0.007) higher in the cetirizine group (84 patients, 90%) than in the placebo group (69 patients, 74%).

The major pollen season began between August 7 and September 26, 1991, for all sites. All patients started treatment within 10 days of each other at each site, and in general between 1 and 2 weeks before the start of the pollen season.

Rhinitis symptoms

The mean changes from baseline for individual rhinitis symptom scores are shown at the top of Fig. 1, and the mean total rhinitis symptom scores are shown at the bottom. All symptoms except nasal congestion showed significant between-group differences at one or more visits. In the cetirizine group there was a reduction (mean change, -1.2) from baseline in the total rhinitis symptom score for week 1, and total symptoms remained near baseline values or below for all weeks of the study (Fig. 1, bottom). In contrast, placebo-treated patients had significant worsening of the total rhinitis symptom score (mean change, +1.4 to +3.6) at all weekly visits as the pollen season began. Cetirizine was significantly better than placebo in maintaining symptom relief at weeks 1 to 4, and the degree of improvement with cetirizine almost reached significance at weeks 5 and 6.

Asthma symptoms

The mean changes from baseline for individual asthma symptom scores are shown at the top of Fig. 2, and the mean total asthma symptom scores are shown at the bottom. Chest tightness, wheezing, shortness of breath, and cough were less severe in the cetirizine group for at least 3 of the 6 weekly visits of treatment. There was significant improvement (mean change, -1.3 to -1.7) in the total asthma treatment score at weeks 1 to 5 for the cetirizine group (Fig. 2, bottom). For all treatment periods except week 3, cetirizine-treated patients had significantly lower total asthma symptom scores than did placebo-treated patients.

There were no significant differences between the two treatment groups with regard to daily measurements of peak flows and weekly pulmonary function parameters. It should be noted that none of these parameters changed with onset of the pollen season.

For each week, the placebo group used more inhalations of albuterol than the cetirizine group, but the differences did not reach statistical significance. The use of pseudoephedrine was similar: 77% of cetirizine-treated and 72% of placebo-treated patients required pseudoephedrine as a rescue medication at least once during the study.

Global evaluations

Both patients and investigators rated cetirizine significantly better than placebo in the global evaluations for rhinitis (3.11 vs 3.55, *p* = 0.042 and 3.14 vs 3.69, *p* = 0.009; patients and investigators, respectively), but the two treatments

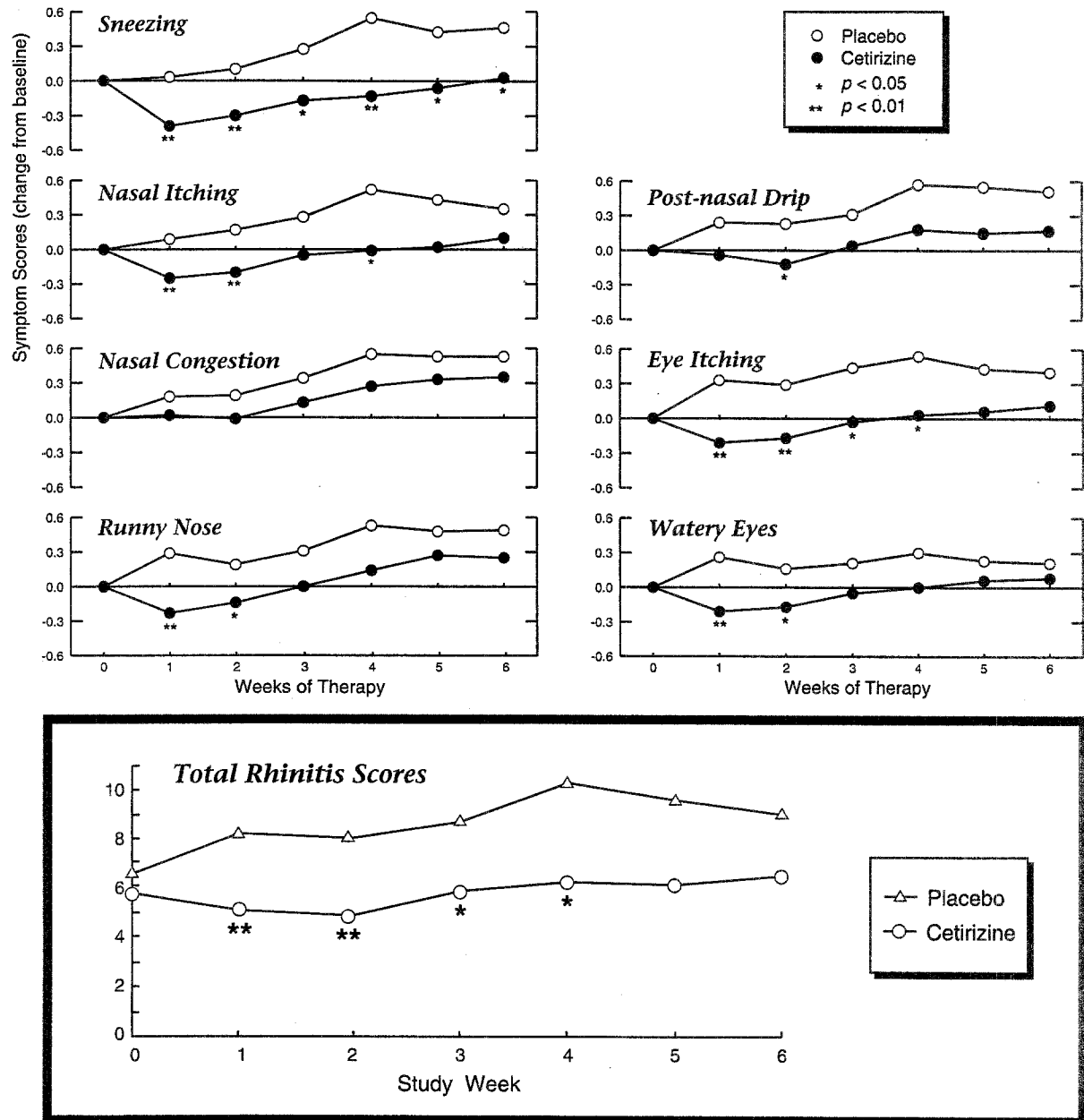


FIG. 1. Individual and total rhinitis symptoms. Significant differences for cetirizine versus placebo groups for each week of evaluation are shown. Alleviation of most symptoms of allergic rhinitis (including sneezing, nasal itching, runny nose, and eye itching) was significantly better with cetirizine than with placebo. There was slight improvement in the mean total rhinitis score (**bottom panel**) from baseline at week 1 in cetirizine-treated patients, and the total score remained near baseline or below after the onset of pollen season for the 6 weeks of the study. In placebo-treated patients, however, the mean total rhinitis score worsened compared with baseline.

were rated similarly for control of asthma (3.22 vs 3.49, $p = 0.18$ and 3.16 vs 3.55, $p = 0.097$). Overall, patients were more satisfied with cetirizine than with placebo ($p = 0.051$).

Safety

The number and percentage of patients reporting adverse experiences was similar in both

groups (46% in the cetirizine group and 48% in the placebo group); the most common complaints are listed in Table II.⁵ The most frequently reported adverse experience was headache, which was similar among treatment groups and predominantly mild to moderate. Although the incidence of fatigue and somnolence was greater with cetirizine than placebo, all cases

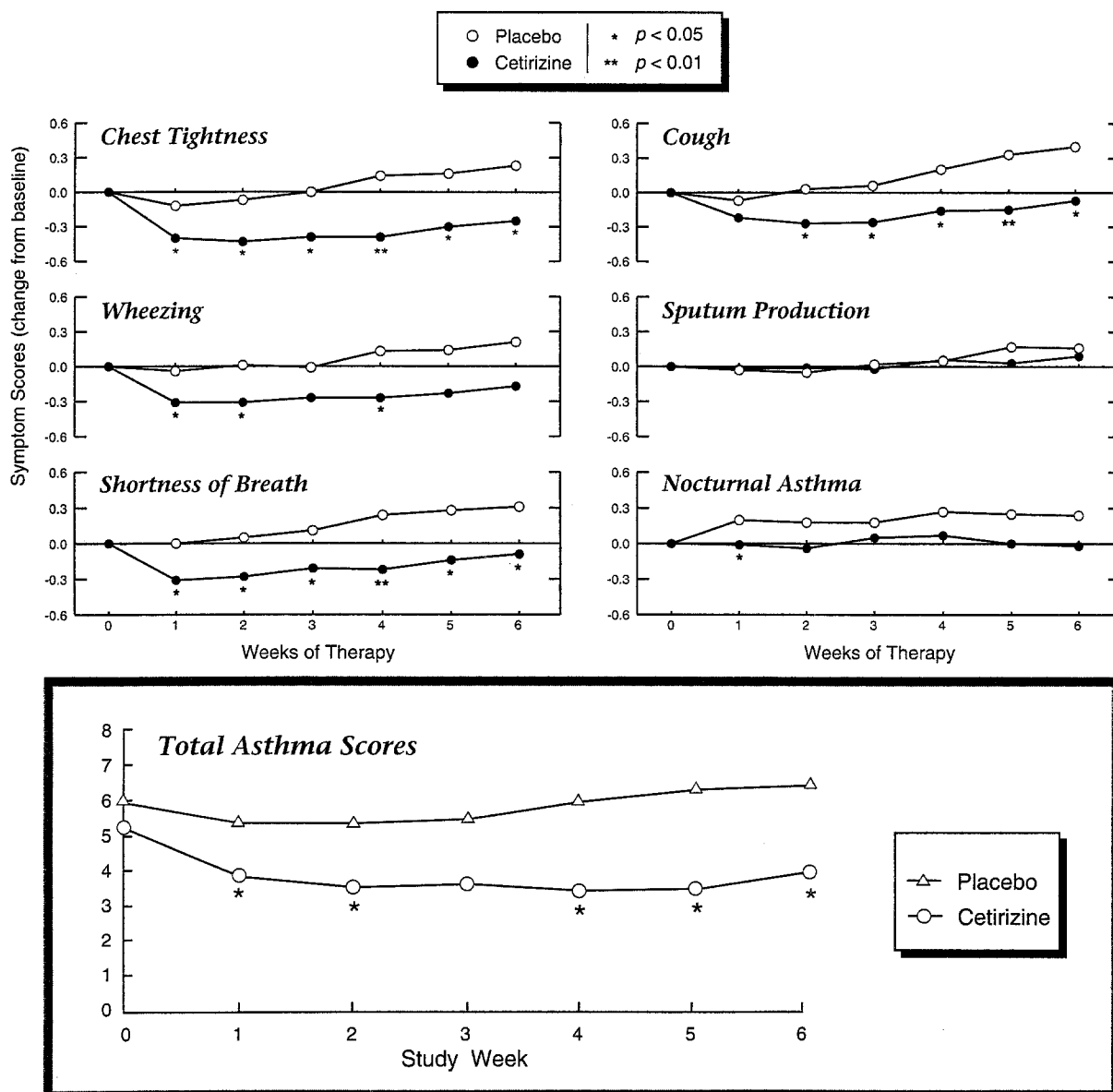


FIG. 2. Individual and total asthma symptoms. Significant differences for cetirizine versus placebo groups for each week of evaluation are shown. Individual asthma symptoms that showed significant improvement in cetirizine-treated patients compared with placebo-treated patients included chest tightness, wheezing, shortness of breath, and cough. The mean total asthma score (**bottom panel**) was significantly improved from baseline at week 1 in patients treated with cetirizine and was significantly better than that in placebo-treated patients for most weeks during the study.

were mild or moderate and did not result in discontinuation of treatment. In addition, no patient in the cetirizine group discontinued treatment because of any adverse experience, and only one patient in the placebo group discontinued because of an adverse experience (joint stiffness, nervousness). There were no clinically significant changes in either group on the basis of physical examinations or laboratory tests.

DISCUSSION

The results of this study confirm the findings of others, which demonstrate that cetirizine 10 mg daily effectively controls or prevents the symptoms of allergic rhinitis.⁴⁶⁻⁴⁸ The significant improvement from baseline in the mean total rhinitis score observed during the first week was sustained after the onset of pollen season (weeks 1 and 2). In contrast, compared with baseline, the mean total rhinitis score worsened in placebo-treated patients

during each week of the study. The differences between treatment groups were significant for weeks 1 to 4. Individual symptoms of rhinitis that were significantly more responsive to cetirizine included sneezing, nasal itching, runny nose, eye itching, and watery eyes.

In this population with allergic rhinitis and mild to moderate asthma, there was significant improvement from baseline in the mean total asthma score, beginning at week 1 in cetirizine-treated patients. For 5 of 6 weeks during the study, the differences between cetirizine and placebo groups in the mean total asthma score were significant. Symptoms of asthma, including chest tightness, wheezing, shortness of breath, and cough, were ameliorated to a significantly greater extent with cetirizine than with placebo. Of particular note is that significantly fewer cetirizine-treated patients withdrew from the study compared with those treated with placebo. These findings are in agreement with other studies that used higher doses of cetirizine and indicate that cetirizine provides symptomatic improvement for both conditions in patients with rhinitis and asthma.^{24-30, 39-41, 43, 44}

There were no differences between the two groups with respect to the results of pulmonary function tests. It should be noted that pulmonary function did not worsen with the onset of the pollen season for either the cetirizine or placebo groups. The lack of a significant effect of cetirizine on pulmonary function may be because the sensitivity of the study was not adequate to detect changes in patients with mild asthma.

A number of studies have assessed the potential benefits of H₁-specific receptor antagonists in patients with clinical asthma but have not provided conclusive findings because of methodologic problems.^{6-8, 18-23, 25-29} Furthermore, most of the studies published to date demonstrating the efficacy of antihistamines in asthma have used higher doses of these drugs than those recommended for treatment of allergy. Two randomized, crossover studies of terfenadine and placebo reported improvements in symptoms and lung function in treated patients who had atopic asthma.^{18, 19} Of importance is that the doses studied (180 mg three times daily and 120 mg twice daily [b.i.d.]) were considerably higher than the recommended dose for treating allergic rhinitis (60 mg b.i.d.), which was shown to have a lesser effect on asthma.⁴⁹ Also, it should be noted that the doses of terfenadine that were required to achieve a significant amelioration of asthma symptoms are now considered contraindicated because of the risk of cardiac arrhythmias

TABLE II. Summary of adverse events

Adverse experiences	No. of patients	
	Cetirizine group	Placebo group
Headache	26*	27
Fatigue	9	1
Somnolence	8	3
Pharyngitis	2	7
Mouth dry	1	4
Total no. of patients reporting adverse events	43	45
No. of adverse events	100	94
Sample size	93	93

*Includes all adverse experiences reported by more than 4% of subjects.

with higher doses.⁵⁰ Howarth⁸ and Howarth and Holgate²⁰ briefly described two studies with small numbers of subjects taking astemizole 10 mg/day. In one group of 14 asthmatic patients,⁸ there were no changes in symptoms, and in the second group²⁰ there was reduction in wheezing, although the full report of this study is not available. Cistero et al.²¹ administered astemizole 10 and 30 mg daily in a crossover study with 12 asthmatic patients, and no changes in symptoms or bronchodilator use were noted. It should be noted that higher doses of astemizole are also associated with cardiac arrhythmias. Kroll et al.²³ evaluated another new antihistamine, loratadine. In an uncontrolled study with 25 patients with allergic asthma, a dose of 10 mg daily for 6 weeks was associated with improved pulmonary function and reduced asthma symptoms and bronchodilator use. However, Dirksen et al.²² evaluated loratadine 10 mg in 17 patients with perennial asthma and failed to record changes in symptoms or peak flow.

Cetirizine has been evaluated previously in comparative studies of pollen-induced asthma.²⁵⁻²⁹ Several studies have used terfenadine 60 mg b.i.d. as control medication for concomitant symptoms of allergic rhinitis, because this dose had been previously found to be ineffective for controlling asthma.^{25, 26, 28} Cetirizine treatment was associated with improvements in symptoms of both allergic rhinitis and asthma, whereas terfenadine treatment was associated with only an improvement in the symptoms of allergic rhinitis. Compared with placebo, higher-dose cetirizine treatment (10 mg b.i.d.) was associated with significant improvements in symptoms and no significant change in pulmonary functions: forced expiratory volume in 1 second or forced vital capacity.²⁷ In previous

reports evaluating cetirizine for treatment of allergic asthma, the doses of cetirizine (10 to 15 mg b.i.d.) evaluated were higher than the usual dose for treatment of allergic rhinitis (10 mg/day), although up to 20 mg daily is indicated for treatment of allergic rhinitis. Lower doses of cetirizine have been considered ineffective in the treatment of asthma.^{6, 44}

The findings of this study are important because the dose of cetirizine studied is the usual dose for treatment of allergic rhinitis, indicating that higher doses may not be necessary to decrease asthma symptoms in patients with allergic rhinitis.

Cetirizine has been shown to block eosinophil migration into the skin after allergen challenge in atopic persons.³⁴⁻³⁶ If cetirizine also blocked eosinophil migration into airways, it would be potentially useful for patients with asthma, because eosinophils have been implicated in bronchial hyperreactivity, which is a characteristic of asthma.¹² Cetirizine 30 mg/kg administered orally to beagle dogs that had been antigen challenged resulted in a significant inhibition of eosinophil influx into the tracheal chamber.⁴² In a human study with a 2-week treatment period, oral cetirizine 10 mg b.i.d. had no significant effect on bronchial hyperreactivity, as assessed by methacholine challenge.²⁴ However, others have found that after 8 days of treatment with cetirizine 15 mg b.i.d., significantly fewer eosinophils were recovered in bronchoalveolar lavage fluid compared with bronchoalveolar lavage fluid from placebo-treated patients.⁴³ Recently, Wasserfallen et al.⁴⁴ reported that the same dose of cetirizine blocked the late-phase asthmatic response to allergen bronchial challenge.

Cetirizine offers several advantages over other minimally sedating antihistamines. Our study confirms that a once daily dose of 10 mg is effective for treatment of both allergic rhinitis and asthma. Simons et al.³² observed that cetirizine was the most potent inhibitor of histamine-induced wheals 24 hours after administration. Van Neste and Rihoux³³ compared the effects of 10 mg each of cetirizine or loratadine. By using laser-Doppler flowmetry recordings, they observed almost complete H₁-histamine receptor blockade in the skin caused by cetirizine, and a lesser effect from loratadine. Wood-Baker and Holgate³¹ observed that cetirizine was the most potent antihistamine in terms of preventing histamine-induced bronchospasm.

Cetirizine is the major metabolite of hydroxyzine. Several investigations have demonstrated that cetirizine is primarily responsible for

the antihistamine actions of hydroxyzine; however, the side effects of hydroxyzine correlate best with the parent compound, hydroxyzine.²⁹ Terfenadine and astemizole are metabolized by the hepatic cytochrome P-450 3A4 enzyme, leading to the potential for multiple drug interactions, especially with antifungal agents and macrolide antibiotics, such as erythromycin and clarithromycin.⁵¹ The simultaneous administration of terfenadine and ketoconazole leads to the accumulation of unmetabolized terfenadine, a drug that inhibits the cardiac delayed rectifier potassium current (I_K channel).^{50, 52} This channel primarily determines the length of the electrocardiographic QT interval during cardiac repolarization, and prolongation of the QT interval is associated with serious arrhythmias and potentially death. Loratadine also accumulates in patients receiving ketoconazole.⁵³ In contrast, cetirizine is not significantly metabolized by the liver, and in doses up to 60 mg daily did not affect the QT interval.⁴⁵

In conclusion, the results of this study confirm the findings of previous studies that cetirizine 10 mg/day is a safe and effective treatment for seasonal allergic rhinitis. In addition, cetirizine treatment controlled asthma symptoms in patients with allergic rhinitis and mild to moderate asthma. These effects in alleviating symptoms of asthma were achieved at the usual dose for treatment of allergic rhinitis. Cetirizine may be considered an additional agent for treating patients with asthma.

We dedicate this article to our colleague, Steve Findlay, who passed away during preparation of the manuscript.

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